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Characterizing the phenotypes of obstructive sleep apnea: Clinical, sleep, and autonomic features of obstructive sleep apnea with and without hypoxia

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HIGHLIGHTS

- We studied the differences between patients with OSA without hypoxia (OSA−h) and OSA with hypoxia (OSA+h).
- Both groups exhibited differences in terms of clinical features, sleep characteristic and cardiac sympathetic modulation during sleep.
- This study suggests that OSA is a heterogeneous disorder and that the differences among OSA subgroups must be considered in future research.

ABSTRACT

Objective: The pathophysiological basis of obstructive sleep apnea (OSA) is not completely understood and likely varies among patients. In this regard, some patients with OSA do not exhibit hypoxemia. We aimed to analyze the clinical, sleep, and autonomic features of a group of patients with severe OSA without hypoxia (OSA−h) and compare to OSA patients with hypoxia (OSA+h) and controls.
Methods: Fifty-six patients with OSA−h, 64 patients with OSA+h, and 44 control subjects were studied. Clinical and sleep features were analyzed. Besides, time- and frequency-domain heart rate variability (HRV) measures comprising the mean R–R interval, the standard deviation of the RR intervals (SDNN), the low frequency (LF) oscillations, the high frequency (HF) oscillations, and the LF/HF ratio, were calculated across sleep stages during a one-night polysomnography.
Results: OSA−h patients had a lower body mass index, a lower waist circumference, lower apnea duration, and a higher frequency of previous naso-pharyngeal surgery when compared to OSA+h patients. In terms of heart rate variability, OSA+h had increased LF oscillations (i.e., baroreflex function) during N1–N2 and rapid eye movement (REM) sleep when compared to OSA−h and controls. Both OSA+h and OSA−h groups had decreased HF oscillations (i.e., vagal inputs) during N1–N2, N3 and REM sleep when compared to controls. The LF/HF ratio was increased during N1–N2 and REM sleep, only in patients with OSA+h.

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Conclusions: Patients with OSA−h exhibit distinctive clinical, sleep, and autonomic features when compared to OSA with hypoxia.
Significance: OSA is a heterogeneous entity. These differences must be taken into account in future studies when analyzing therapeutic approaches for sleep apnea patients.

1. Introduction

Obstructive Sleep Apnea (OSA) is a sleep breathing disorder that affects over 5% of men and 2% of women (Parati et al., 2007). OSA, which is considered an independent risk factor for cardiovascular disease (Bradley and Floras, 2009), is characterized by repetitive episodes of partial or complete closure of the upper airway which give rise to hypoxemia, changes in intrathoracic pressure, surges in sympathetic activity, and changes in the heart rate regulation (Hakim et al., 2012). The repetitive nature of apneas and the arousal events result in significant sleep fragmentation and sleepiness, and may contribute to arrhythmia and cardiac sudden death (McNicholas et al., 2007).

The pathophysiology of OSA is not completely understood (Eckert and Malhotra, 2008). Arousal from sleep at the cessation of an apnea or hypopnea is considered a key protective mechanism for airway reopening (Remmers et al., 1978). In fact, most respiratory events are associated with cortical arousals and more severe events result in longer arousals (Nigro and Rhodius, 2005). However, the intuitive idea that the breakpoint breath and the arousals after the apneas are a direct consequence of hypoxia is not accurate, given that other mechanisms, such as the level of pleural pressure (Gleeson et al., 1990), and the activity of inspiratory muscles/diaphragm (Vincken et al., 1987; Parkes, 2006), generated by increased respiratory effort during the obstructive apneas (regardless of the degree of hypoxia), are probably the key triggers for inducing arousal.

The existence of a particular subgroup of OSA patients without hypoxia (OSA−h) with significant sleep fragmentation and sleepiness seems to corroborate this idea. Patients with OSA without hypoxia are occasionally seen on the sleep clinic. However, the physiopathologic mechanisms by which these patients have normal oxygen saturation in spite of the apneas are unknown. With the exception of a study focusing on the severity of cognitive impairment in patients with OSA with and without hypoxia (Findley et al., 1986), features of OSA−h have not been comprehensively studied yet, so it is unknown whether this group of patients exhibits any distinctive features in terms of pathophysiologic mechanisms when compared to OSA with hypoxia (OSA+h).

There is evidence that the autonomic nervous system (ANS) is dysregulated during sleep and wakefulness in OSA patients, even in those without cardiovascular disease. When heart rate variability (HRV) during sleep is studied, OSA patients exhibit increased sympathetic and decreased parasympathetic modulations (Gula et al., 2003; Jo et al., 2005). CPAP therapy seems to reverse these changes, even in the first night of treatment (Kufoy et al., 2012). Besides, there is increasing evidence that points to hypoxia (and not to the apneas) as the main etiopathogenic factor for the cardiac autonomic impairment seen in OSA (Hakim et al., 2012; Palma et al., 2013). In this regard, OSA−h patients represent a uniquely valuable group of subjects to explore this question, as they have significant respiratory events during sleep, but oxygen desaturations are virtually absent. We hypothesized that, if HRV changes are a consequence of hypoxemia (and not a consequence of the changes in intrathoracic pressure during respiratory events), cardiac autonomic tone during sleep should be less impaired in patients with OSA−h than those with OSA+h.

This study aimed to analyze, first, the clinical and sleep features of a group of patients with OSA−h and compare it with a group of OSA+h patients and control subjects. And second, it also intended to evaluate the autonomic cardiovascular function during sleep in OSA−h patients using time- and frequency-domain HRV analysis during one-night polysomnography (PSG).

Deepening our understanding in the clinical, sleep and autonomic features of OSA−h patients may offer a valuable insight into the physiopathology of sleep related breathing disorders and into the relevance of hypoxia in the cardiac autonomic dysregulation, which may provide a better understanding for the development of novel therapeutic approaches that target underlying mechanisms of individual OSA patients.

2. Methods

2.1. Subjects

Subjects with severe OSA, defined as apnea/hypopnea index (AHI) > 30 events/h of sleep, were consecutively recruited during a 1-year period, between February 2012 and February 2013. Other than OSA, participants were healthy and were not taking any medication known to affect sleep or other parameter measured in the first part of the study. Informed written consent, as approved by the Institutional Review Board (IRB) of the University of Navarra, was obtained.

The first aim of this study was to define whether there exist any differences in term of clinical and polysomnographic features between OSA−h and OSA+h patients. Patients with OSA−h were selected if they fulfilled the following inclusion criteria: (i) AHI > 30 events/h of sleep; (ii) PSG showing a minimal $SatO_2$ > 88%; (iii) more than 80% of total sleep time with a $SatO_2$ > 96%; (iv) age between 35 and 75.

Inclusion criteria for OSA+h patients (i.e., OSA with hypoxia) comprised: (i) AHI > 30 events/h of sleep; (ii) PSG showing a minimal $SatO_2$ < 88%; (iii) less than 80% of total sleep time with a $SatO_2$ > 96%; (iv) age between 35 and 75.

Inclusion criteria for control subjects comprised: (i) AHI < 5 events/h of sleep; (ii) PSG showing a minimal $SatO_2$ > 88%; (iii) more than 80% of total sleep time with a $SatO_2$ > 96%; (iv) age between 35 and 75; (v) absence of snoring.

Our second objective was to ascertain whether the cardiac autonomic impairment across sleep stages was different between OSA+h and OSA−h as measured by HRV. Given that HRV can be influenced by several factors, we excluded certain patients from the initial cohort to ensure the accuracy of HRV results. Patients were excluded from the HRV analysis if they had a history of: (i) atrial fibrillation and other cardiac arrhythmias; (ii) myocardial ischemia, cardiomyopathy or myocardial infarction; (iii) cardiac pacemaker; (iv) history of neurologic disorders (including stroke, epilepsy, demyelinating disorders, dementia, movement disorders, migraine and trigeminal-autonomic cephalalgias, as these conditions have been associated with abnormal cardiac autonomic tone); (v) history of psychiatric or functional disorders (such as irritable bowel syndrome, chronic fatigue syndrome, and fibromyalgia); (vi) diabetes mellitus or thyroid diseases; (vii) other sleep

disorders such as periodic limb movements (PLMS), restless limb syndrome (RLS), upper airway resistance syndrome (UARS), or narcolepsy; and (viii) treatment with calcium channels blocker, β-blockers, or any other drugs known to affect the ANS.

2.2. Data acquisition and handling

OSA was diagnosed based on an overnight PSG study. PSG studies were performed using Lamont amplifiers, 20 bit, 32 channels and dedicated inputs for EEG, electrooculogram, tibial and chin EMG, oronasal flow, respiratory effort, oxymetry, heart rate and body position. A nasal pressure transducer was used to detect UARS. Sleep stage classification was performed following the current American Academy of Sleep Medicine (AASM) criteria (Silber et al., 2007), and hypopneas, apneas and arousals were scored using the standard recommended AASM scoring criteria (American Academy of Sleep Medicine, 2007). We recorded data on the following features: total sleep time; sleep latency; percentage of sleep spent in rapid eye movement (REM) sleep, N1 (somnolence, characterized by loss of some muscle tone and some conscious awareness of the external environment), N2 (sleep stage characterized by sleep spindles and K-complexes in which conscious awareness of the external environment disappears), and N3 (deep or slow-wave sleep characterized by the presence of delta waves); REM latency; wake time after sleep onset (WASO); number of awakenings per hour; number of arousals per hour; mean oxygen saturation ($SatO_2$); minimal $SatO_2$; AHI; and duration of apnea.

2.3. HRV data handling and analysis

For each patient, we carefully selected several, consecutive apnea-free, awakening-free, 10-min ECG samples, from each sleep stage (REM, N1–N2, N3 and wakefulness before sleep [W-pre] and after sleep [W-post]). ECG was recorded with two derivations (V3 and V5), amplified, band-pass filtered (0.3–30 Hz), and digitized at 250 Hz.

Sleep data in the form of digital files were collected using the Stellate Reviewer software program (Harmonie 6.0). The sleep segments were saved as text files from their digital recording in Stellate Reviewer Version 6 (Stellate Inc., Montreal Canada). The text files containing the sleep data were converted into a Spike2 data file (S2R) using Spike2 (version 6.02, Cambridge Electronic Design Limited, Cambridge, UK). Then, two of the authors (JAP, EU) performed the HRV of each patient blinded to the PSG results using the S2R files in a HRV analysis program created with MatLab (Mathworks Inc., Natick Massachusetts, USA) by one of the authors (MV). The MatLab analysis program identified the R waves of each ECG recording and calculated the time- and frequency-domain measures by using a Welch averaged periodogram method. Each ECG recording was manually inspected to avoid abnormal QRS wave morphology, ectopic cardiac beats, movement artifacts, and to ensure that R-waves were correctly marked by the HRV analysis program to allow an accurate detection of R–R intervals.

The following heart rate variability measures were computed in the time and frequency domain based on the measurement standards (Task Force, 1996):

2.3.1. Time domain measures

- Mean R–R: the mean normal-to-normal RR interval, in s.
- SDNN: the standard deviation of normal-to-normal RR intervals, which reflects the overall heart rate variability, in ms.

2.3.2. Frequency-domain measures

For HRV analysis in the frequency domain, the beat series derived from the 5-min ECG segments were interpolated to obtain equally spaced RR intervals and to assess the 1024-point spectra (interpolation rate of 3.41 Hz). Then, Welch's periodogram and fast-Fourier transform (FFT) was applied. The length of the FFT was a 1024-sample window, with 75% overlap. We quantified HRV power in two power spectrum density (PSD) bands:

- LF band (low frequency power in the range of 0.04–0.15 Hz), in ms^2, which reflects a combination of sympathetic and parasympathetic influences represented in the baroreflex function (Goldstein et al., 2011).
- HF band (high frequency power in the range of 0.15–0.40 Hz), in ms^2, which reflects the respiratory sinus arrhythmia function, predominantly modulated by the parasympathetic system.

We also considered the LF/HF ratio, a unitless measure that is thought to reflect the sympathovagal balance. Thus, a higher LF/HF would indicate a predominance of sympathetic modulations (Task Force, 1996). This ratio was used rather than normalized LF and HF values as the normalized val ues are mathematically equivalent to the LF/HF ratio and do not add any information over and above that measure (Burr, 2007).

Also, as nonlinear parameter, we calculated the Approximate Entropy (ApEn). Measures of entropy quantify the complexity of heart rate dynamics (Task Force, 1996). Lower values of entropy reflect more predictable data and more random data are described by higher values of entropy. ApEn a measure of complexity of real data sequences (Pincus, 1991). Assessment of ApEn was performed with the same MatLab custom software using methods described elsewhere (Richman and Moorman, 2000) with so called values $m = 2$ and $r = 0.2 \times$ SD of R–R intervals were used.

2.4. Statistical analyses

Comparisons of patients' characteristics and sleep characteristics in the three samples were performed by using ANOVA, with Bonferroni's correction for multiple comparisons as post-hoc analysis, and the interaction where appropriate. For the comparison of HRV results we used the non-parametric ANOVA Kruskal–Wallis test. In all cases, statistical significance was defined as $p < 0.05$. All statistical tests were performed using SPSS version 15.0.1 (SPSS Inc., Chicago, IL, USA).

3. Results

3.1. Subjects characteristics

Fifty-six OSA−h patients (4 women), 64 OSA+h patients (8 women), and 44 controls (8 women) were included. All groups had similar age and sex proportions. Patients with OSA+h tended to have a higher BMI, compared with OSA−h and controls ($p = 0.008$). OSA+h and OSA−h patients had an increased cervical circumference when compared with controls ($p = 0.026$). Similarly, OSA+h patients had an increased waist circumference when compared to OSA−h and controls; waist circumference in OSA−h was also higher that controls ($p = 0.002$). Interestingly, 20 patients with OSA−h (in contrast to no patients in the OSA+h or control groups) had previously undergone ENT surgery, comprising uvulopharyngopalatoplasty in 12, amygdalectomy in 8, and turbinate surgery with septoplasty in 12. Demographic characteristics of OSA−h, OSA+h and controls are summarized in Table 1.

3.2. Sleep characteristics

Sleep structure, including REM latency, percentage of REM, N2 and N3 sleep, was similar in all groups except for percentage of N1 sleep, higher in OSA−h patients when compared to OSA+h

Table 1
Sample characteristics.

	OSA−h (n = 56)	OSA+h (n = 64)	Controls (n = 44)	ANOVA F value	ANOVA p value
Age (y), mean ± SD	54.29 ± 9.77	51.19 ± 10.41	49.09 ± 12.15	2.02	0.36
Women, n (%)	4 (7.1%)	8 (12.5%)	8 (18.2%)	N/A	0.70
BMI (kg/m^2)	28.49 ± 5.95	34.81 ± 7.78	27.4 ± 3.79	23.14	**0.008**
Neck circumference (cm)	42 ± 3.24	43.71 ± 3.71	39 ± 4.84	9.04	**0.026**
Waist circumference (cm)	102.75 ± 10.52	118.32 ± 15.19	96.65 ± 15.09	36.84	**0.002**
Blood pressure (mm Hg)					
Systolic	121.36 ± 6.67	124.31 ± 13.29	118.59 ± 13.02	2.34	0.22
Diastolic	75 ± 7.92	72.54 ± 8.08	75.72 ± 9.18	1.25	0.31
Previous ENT surgery, n (%)	20 (35.7%)	0	0	N/A	**<0.001**

OSA−h: obstructive sleep apnea without hypoxia; OSA+h: obstructive sleep apnea with hypoxia; SD: standard deviation; BMI: body mass index. Values in bold denote a statistically significant result ($p < 0.05$).

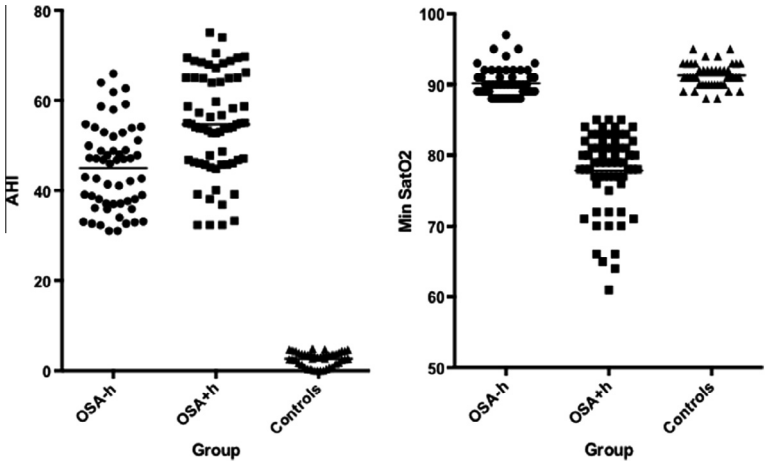

Fig. 1. Individual values of apnea hypopnea index (AHI) and minimum oxygen saturation ($SatO_2$) in patients with OSA−h patients, OSA+h patients, and control subjects. AHI was similar in OSA+h and OSA−h, and lower in controls. However, the Min $SatO_2$ was similar in controls and OSA−h and lower in OSA+h.

Table 2
Sleep characteristics in OSA−h patients, OSA+h patients, and control subjects.

	OSA−h (n = 56)	OSA+h (n = 64)	Controls (n = 44)	ANOVA F value	ANOVA p value
Sleep latency (min)	14 ± 12	13 ± 11	18 ± 14	2.22	0.11
REM latency (min)	124.93 ± 74.02	128.47 ± 90.04	107.5 ± 68.83	0.98	0.79
TST (min)	454.57 ± 60.88	472.75 ± 69.99	436.91 ± 54.61	2.26	0.072
Awakenings (n°/h)	14.79 ± 6.05	8.81 ± 3.76	9.45 ± 5.71	2.17	0.10
REM stage (%)	18.91 ± 6.87	17.69 ± 6.56	20.70 ± 5.41	2.09	0.15
N1 stage (%)	4.40 ± 2.54	2.04 ± 2.12	1.53 ± 1.61	17.81	**0.049**
N2 stage (%)	54.37 ± 7.45	57.91 ± 15.51	50.73 ± 8.01	2.16	0.29
N3 stage (%)	22.30 ± 6.71	23.44 ± 14.82	27.81 ± 11.73	1.92	0.49
WASO (%)	16.03 ± 10.39	9.32 ± 7.66	11.12 ± 8.16	2.10	0.12
AHI (n°/h)	48.35 ± 12.5	53.08 ± 11.97	2.99 ± 1.84	85.15	**<0.001**
Apnea duration (s)	21.45 ± 5.13	27.35 ± 5.43	13.59 ± 5.45	24.69	**<0.001**
Minimal $SatO_2$ (%)	90.86 ± 1.83	78.13 ± 5.29	91.18 ± 1.47	69.94	**<0.001**
Mean $SatO_2$ (%)	95.79 ± 1.71	94.31 ± 1.95	96.36 ± 1.20	6.27	**0.009**
Sleep time spent with $SatO_2$ 96–100% (%)	88.23 ± 6.38	51.26 ± 25.13	89.78 ± 7.38	27.37	**<0.001**
Sleep time spent with $SatO_2$ 90–95% (%)	9.86 ± 6.55	37.66 ± 19.92	10.2 ± 13.38	19.82	**<0.001**
Arousals (n°/h)	132.86 ± 24.31	165.27 ± 31.35	24.86 ± 12.81	108.4	**<0.001**

OSA−h: obstructive sleep apnea without hypoxia; OSA+h: obstructive sleep apnea with hypoxia; SD: standard deviation; WASO: wake time after sleep onset; AHI: apnea–hypopnea index. Values in bold denote a statistically significant result ($p < 0.05$).

and control subjects ($p = 0.05$). As anticipated, OSA+h and OSA−h patients had a higher AHI when compared with control subjects ($p < 0.001$). OSA−h and controls had a similar mean and minimal $SatO_2$, but higher when compared to OSA+h patients ($p < 0.001$). Fig. 1 depicts the distribution of AHI and minimal $SatO_2$ among groups. Arousals were more frequent in OSA+h and OSA−h when compared with controls ($p < 0.001$). Apnea duration was longer in OSA+h and OSA−h than in controls ($p < 0.001$). Apnea duration was also longer in OSA+h when compared to OSA−h ($p = 0.032$). The awakening index tended to be higher in OSA−h patients, although differences were not statistically significant. Sleep characteristics of all groups are summarized in Table 2.

To check whether differences in age, BMI or prevalence in arterial hypertension had any influence on the sleep characteristics in our sample, we also performed an analysis of covariance (data not shown). Significant differences remained unchanged.

Table 3
Characteristics of patients selected for HRV analysis.

	OSA−h (n = 33)	OSA+h (n = 37)	Controls (n = 36)	ANOVA F value	ANOVA p value
Age (y), mean ± SD	52.77 ± 10.71	50.21 ± 8.71	50.76 ± 7.49	0.37	0.82
Women, n (%)	3 (9%)	6 (16%)	6 (16%)	N/A	0.45
BMI (kg/m^2)	27.31 ± 4.21	28.44 ± 5.97	27.43 ± 4.02	0.27	0.37
AHI (n°/h)	44.31 ± 9.81	48.53 ± 8.98	1.27 ± 1.84	129.2	**<0.001**
Apnea duration (s)	20.31 ± 4.15	26.51 ± 5.02	12.87 ± 4.52	32.32	**<0.001**
Minimal $SatO_2$ (%)	91.32 ± 1.39	76.98 ± 6.26	92.12 ± 1.43	68.85	**<0.001**
Mean $SatO_2$ (%)	95.84 ± 1.44	94.41 ± 1.92	96.16 ± 1.33	5.5	**0.008**
Sleep time spent with $SatO_2$ 96–100% (%)	89.12 ± 4.88	54.31 ± 19.85	89.82 ± 6.41	37.99	**<0.001**
Sleep time spent with $SatO_2$ 90–95% (%)	9.96 ± 5.43	39.48 ± 13.92	10.1 ± 9.27	36.88	**<0.001**

OSA−h: obstructive sleep apnea without hypoxia; OSA+h: obstructive sleep apnea with hypoxia; SD: standard deviation; BMI: body mass index. Values in bold denote a statistically significant result (p < 0.05).

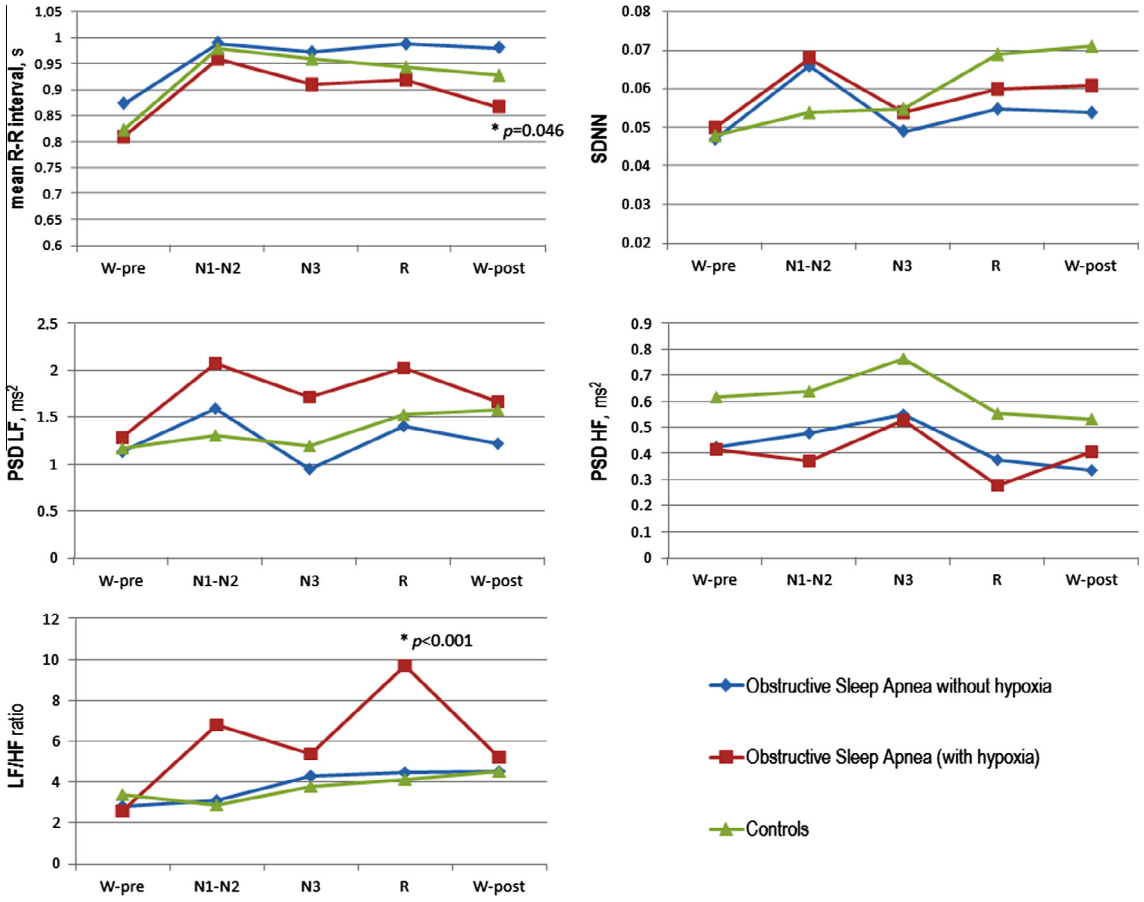

Fig. 2. Mean R–R interval, standard deviation of the NN interval (SDNN), low-frequency composnents (LF) and high frequency components (HF) during different sleep stages (N1–N2, N3, REM) as well as during wakefulness before (W-pre) and after (W-post) sleep in OSA−h patients, OSA+h patients, and control subjects. Asterisks (*) indicate statistical significance, and the Kruskal Wallis p-value is given.

3.3. Heart rate variability analysis

Thirty-three OSA−h patients (3 women), 37 OSA+h patients (6 women), and 36 controls (6 women) fulfilled the inclusion criteria for HRV analysis. This subgroup of patients selected for HRV analysis had similar age, BMI, and sleep structure that the initial group of patients (data not shown). The most common reasons to exclude patients from the initial groups were treatment with calcium channels blocker, β-blockers, or any other drugs known to affect the ANS (6 patients with OSA−h, 11 with OSA+h and 3 controls), diabetes mellitus (5 patients with OSA−h, 6 with OSA+h and 2 controls) and arrhythmia (3 patients with OSA−h, 7 with OSA+h and 1 control). As shown in Table 3, the three groups resulted to have similar gender, age, and BMI. As expected, AHI and apnea duration were higher in OSA+h and OSA−h when compared to controls.

The mean R–R interval was similar in patients with OSA−h, OSA+h and controls in all sleep stages, except in W-post, where R–R interval was significantly lower in OSA+h when compared to the remaining groups (p = 0.046). No significant differences were observed in the SDNN.

Regarding the spectral components of the HRV, the LF band displayed an increased power in OSA+h patients during N1–N2 (p = 0.032) and REM (p = 0.031) when compared to OSA−h and controls. This band was also higher during N3 in OSA, although the p value was not significant.

Table 4
Heart rate variability across sleep stages in OSA without hypoxia patients, OSA with hypoxia patients and control subjects. *p* Value corresponds to statistical significance in the Kruskal–Wallis test ($p < 0.05$).

	W-pre	*p*	N1–N2	*p*	N3	*p*	REM	*p*	W-post	*p*
Mean R–R interval, ms ± SD										
OSA without hypoxia	873 ± 84	0.18	991 ± 112	0.80	974 ± 114	0.08	988 ± 105	0.67	981 ± 120	**0.046**[a]
OSA with hypoxia	810 ± 104		962 ± 112		910 ± 94		919 ± 120		867 ± 68	
Controls	823 ± 95		983 ± 110		960 ± 90		944 ± 92		929 ± 76	
SDNN, ms ± SD										
OSA without hypoxia	0.04 ± 0.02	0.89	0.066 ± 0.03	0.23	0.049 ± 0.02	0.92	0.055 ± 0.02	0.57	0.054 ± 0.02	0.49
OSA with hypoxia	0.05 ± 0.02		0.068 ± 0.04		0.054 ± 0.03		0.060 ± 0.02		0.061 ± 0.03	
Controls	0.04 ± 0.02		0.054 ± 0.02		0.055 ± 0.02		0.069 ± 0.02		0.071 ± 0.02	
LF, ms^2 ± SD										
OSA without hypoxia	1.14 ± 1.55	0.98	1.60 ± 0.23	**0.032**[b]	0.95 ± 0.75	0.44	1.41 ± 0.2	**0.031**[c]	1.23 ± 0.82	0.70
OSA with hypoxia	1.29 ± 1.55		2.07 ± 0.42		1.73 ± 0.91		2.03 ± 0.4		1.68 ± 1.04	
Controls	1.18 ± 1.26		1.31 ± 0.48		1.21 ± 0.57		1.53 ± 0.2		1.58 ± 0.98	
HF, ms^2 ± SD										
OSA without hypoxia	0.43 ± 0.39	0.76	0.48 ± 0.19	**0.048**[d]	0.55 ± 0.17	**0.027**[e]	0.38 ± 0.14	**0.035**[f]	0.34 ± 0.25	0.40
OSA with hypoxia	0.42 ± 0.22		0.37 ± 0.08		0.53 ± 0.07		0.28 ± 0.07		0.41 ± 0.29	
Controls	0.62 ± 0.34		0.64 ± 0.18		0.77 ± 0.13		0.56 ± 0.18		0.53 ± 0.30	
LF/HF ratio, ± SD										
OSA without hypoxia	2.85 ± 1.51	0.44	2.13 ± 0.21	**0.018**[g]	4.32 ± 2.5	0.24	4.51 ± 2.18	**<0.001**[h]	4.57 ± 1.33	0.63
OSA with hypoxia	3.60 ± 1.75		6.82 ± 1.52		5.42 ± 2.9		9.75 ± 1.93		5.24 ± 1.38	
Controls	2.45 ± 1.65		2.90 ± 1.71		3.83 ± 2.2		4.19 ± 1.04		4.58 ± 1.41	
ApEn, ± SD										
OSA without hypoxia	1.134 ± 0.154	0.91	1.154 ± 0.198	0.84	1.141 ± 0.139	0.92	1.221 ± 0.144	**0.002**[i]	1.131 ± 0.14	0.63
OSA with hypoxia	1.121 ± 0.121		1.161 ± 0.168		1.125 ± 0.181		1.279 ± 0.125		1.128 ± 0.12	
Controls	1.129 ± 0.126		1.139 ± 0.114		1.135 ± 0.177		1.145 ± 0.198		1.127 ± 0.15	

[a] Mean R–R interval post-hoc comparisons that resulted significant after Bonferroni's post-hoc test: OSA with hypoxia vs OSA without hypoxia.
[b] LF during N1–N2 post-hoc comparisons that resulted significant after Bonferroni's post-hoc test: OSA with hypoxia vs OSA without hypoxia; OSA with hypoxia vs controls.
[c] LF during REM post-hoc comparisons that resulted significant after Bonferroni's post-hoc test: OSA with hypoxia vs OSA without hypoxia; OSA wth hypoxia vs controls.
[d] HF during N1–N2 post-hoc comparisons that resulted significant after Bonferroni's post-hoc test: Controls vs OSA without hypoxia; Controls vs OSA with hypoxia.
[e] HF during N3 post-hoc comparisons that resulted significant after Bonferroni's post-hoc test: Controls vs OSA without hypoxia; Controls vs OSA with hypoxia.
[f] HF during REM post-hoc comparisons that resulted significant after Bonferroni's post-hoc test: Controls vs OSA without hypoxia; Controls vs OSA with hypoxia.
[g] LF/HF ratio during N1–N2 post-hoc comparisons that resulted significant after Bonferroni's post-hoc test: OSA with hypoxia vs OSA without hypoxia; OSA with hypoxia vs controls.
[h] LF/HF ratio during REM post-hoc comparisons that resulted significant after Bonferroni's post-hoc test: OSA with hypoxia vs OSA without hypoxia; OSA with hypoxia vs controls.
[i] ApEn during REM post-hoc comparisons that resulted significant after Bonferroni's pot-hoc test: OSA with hypoxia vs. controls.

In the HF band, the power in OSA−h and OSA+h patients was significantly lower than in controls in N1–N2 ($p = 0.048$), N3 ($p = 0.027$) and REM ($p = 0.035$) but not during W-pre and W-post.

The LF/HF ratio was significantly higher in OSA+h patients during N1–N2 ($p = 0.018$) and REM sleep ($p < 0.001$), when compared to OSA−h and control subjects. (Fig. 2)

Finally, ApEn was significantly higher in OSA+h patients during REM ($p = 0.002$) when compared to controls (Table 4).

4. Discussion

In this work, we aimed to study the features of a group of OSA−h patients, and to compare it with a sample of OSA+h patients and control subjects. Another of our aims was to investigate the cardiac autonomic tone across sleep stages in a homogeneous sample (free from medications, co-morbidities and any other concurrent sleep disorders) of well-matched groups of OSA−h patients, OSA+h patients, and control subjects. To the best of our knowledge, this is the first study that takes into account the fact that some patients with OSA have no hypoxia, and attempt to analyze the differences between the two types of OSA.

Our results revealed that OSA−h patients exhibit certain different features when compared to OSA+h patients. Indeed, OSA−h patients had a lower BMI and waist circumference, as previously observed (Peppard et al., 2009). However, both groups of patients had a similar neck circumference, but higher than control subjects. Interestingly, a noteworthy proportion of OSA−h patients (~40%) had previously undergone nasal, laryngeal or pharyngeal surgery, in contrast to OSA+h and control patients. As expected, OSA+h and OSA−h had similar AIH index (higher than controls), and OSA+h had lower mean and minimum $SatO_2$ when compared to OSA−h and controls.

According to the American Academy of Sleep Medicine, the objective diagnosis of OSA is confirmed if the number of obstructive events on PSG is greater than 15 events/h or greater than 5/h in a patient who reports poor sleep quality or excessive daytime sleepiness (Epstein et al., 2009). There are no specific allusions to the degree of hypoxia. Thus, we relied upon two criteria to define "OSA with hypoxia": First, we chose a cutoff at minimal $SatO_2$ below 88%. This measure provided a quantification of severity. However, given that the minimal saturation measures the magnitude of a single desaturation to characterize a whole night of sleep, we also took the percentage of sleep time in which $SatO_2$ was 96% or higher. This second measure guaranteed that the hypoxia was not an isolated phenomenon but rather a prolonged situation during the whole sleep. As expected, control subjects and OSA−h patients were similar regarding these two measures.

4.1. Implications for the physiopathology of sleep apnea

Taken together, all these data suggest that the mechanisms of apneas and hypopneas may be not completely dependent on biomechanical features (i.e., upper respiratory airway and abdominal configuration), but rather to a decreased sensitivity in respiratory mechanoreceptors (i.e., pulmonary or diaphragmatic afferents) (Gleeson et al., 1990; Parkes, 2006). In this stage, the breath-holding during apnea would increase the central respiratory rhythm,

giving rise to a breakpoint breath, particularly in patients with an oversensitive ventilatory control system (i.e., high loop gain) (Wellman et al., 2004). In fact, recent data suggest that the loop gain might be relevant in OSA pathogenesis in those patients with mild vulnerability to upper-airway collapse (Eckert et al., 2013). In this regard, there is evidence that, in patients with OSA−h, the closure of the upper airway can be partial, even in spite of the fact that the nasal thermistor detects a full apnea (Iriarte et al., 2013). Thus, the loop gain would be increased in OSA−h when compared to OSA+h patients. This factor would also contribute to the avoidance of hypoxia during the apneic episodes in OSA−h patients.

The addition of certain biomechanical features (e.g., narrow upper respiratory airway, and abdominal obesity that increase upper airway collapsibility) would contribute to close the airway completely, increase the length of apnea, decrease the arousal threshold, and lead to a longer time to the breakpoint breath (i.e., decreased loop gain) which, at the end, would result in hypoxia (Richter et al., 1993). This notion is supported by two of our findings: First, apnea duration was longer in patients with OSA+h when compared to OSA−h; and second, subjects with OSA−h had more awakenings than subjects with OSA+h. In this regard, our results confirm recent data showing that OSA patients have an increased arousal threshold (i.e., waking up prematurely to airway narrowing) (Eckert et al., 2013) and contribute to them by showing that OSA−h patients may have a higher respiratory arousal threshold when compared to OSA+h patients.

4.2. Differences in cardiac autonomic tone between OSA−h and OSA+h

In terms of cardiac autonomic tone, our results revealed that OSA−h patients tended to have similar LF heart rate oscillations (which reflect the baroreflex function mediated by both sympathetic and parasympathetic inputs) to controls; and decreased HF heart oscillations (which are modulated by parasympathetic inputs only) when compared to controls. These results indicate a dysregulation only in parasympathetic modulations (i.e., HF band) in OSA−h patients, similar to that observed in OSA+h. However, in OSA−h, the the LF/HF ratio the LF modulations were similar to those observed in controls, in contrast to the significant increases of the LF/HF ratio and LF modulations observed in OSA+h, predominantly during REM sleep. The sympathetic contribution to the LF/HF ration and the LF modulations might be the source of difference in OSA+h, thus suggesting that hypoxia (and not apneas) triggers increases in sympathetic tone.

The non-linear parameter ApEn was increased in patients with OSA+h when compared to controls (but not in OSA−h), suggesting that the hypoxia contributes to the entropy (i.e., the unpredictability of fluctuations) of the HRV. Interestingly, these results were unrelated to gender, age or BMI, as the three groups were well matched in terms of these features. Our results are mainly in accordance with previous reports which established that hypoxemia elevates the basal sympathetic tone (Foster et al., 2009), and that OSA+h patients have an increased sympathetic tone during sleep (Dingli et al., 2003). Similar findings (i.e., increased LF modulations and LF/HF ratio during sleep) have been described in patients with sleep related alveolar hypoventilation (SRAH) (Palma et al., 2013), a condition characterized by decreased alveolar ventilation resulting in sleep related oxygen desaturations in patients with normal mechanical properties of the lung (American Academy of Sleep Medicine, 2005). Apneas and hypopneas are not typically present in SRAH, which emphasizes the role of hypoxia *per se*, independently of other phenomena, in the pathogenesis of the cardiac autonomic and hemodynamic stress observed in patients with sleep-disordered breathing, particularly in the increased sympathetic tone (Gottlieb et al., 2009; Palma et al., 2013).

4.3. Role of the parasympathetic nervous system

The individual effects of intermittent hypoxia and intrathoracic pressure swings on the autonomic nervous system activity during sleep-disordered breathing are difficult to disentangle (Hakim et al., 2012). In this regard, we added further insight into the pathophysiology of abnormal autonomic tone during sleep observed in OSA patients. Our results suggest that an initial decreased parasympathetic tone (i.e., decreased HF oscillations, as seen in OSA with and without hypoxia) might be unrelated to the hypoxia during sleep but linked to the apneas themselves. In latter stages, the increased sympathetic tone (which might contribute to an augmentation of the sympathetic component of the LF/HF ratio and the LF modulations, which is observed only in OSA with hypoxia) might be a direct consequence of the hypoxia during sleep.

The relationship between the apneas and the changes in the parasympathetic modulations presumably relies upon the afferent fibers from the pulmonary (including stretch receptors, irritant receptors, and J receptors) and diaphragmatic receptors that arrive at the pons via the vagus nerve. Indeed, classic experiments showed that blockade of the vagus nerve leads to a significant prolongation of the breath-hold duration (Guz et al., 1970; Harty et al., 1996). In fact, HF heart rate oscillations are intimately linked to the respiratory sinus arrhythmia (RSA), a physiologic phenomenon that reflects the coupling of centrally generated respiratory and cardiovascular efferent activities.

4.4. The continuum of OSA

Although additional research is required, we hypothesize that our results may reflect a continuum with two possibilities. In the first one, subjects with a genetically predetermined mechanoreceptor function and/or increased loop gain would develop apneas, but not hypoxia. With the concurrency of additional biomechanical factors, the arousal threshold and the length of apneas would increase in certain subjects, together with a blunting of the awakening response to neural stimuli produced during obstructed inspiratory effort (i.e., decreased loop gain), eventually giving rise to hypoxia. While the apneas would initiate the impairment in the parasympathetic modulations (reflected by the HF band; via the mechanoreceptor afferents, as seen both in OSA−h and OSA+h patients), the hypoxia *per se* would predominantly trigger the surges in sympathetic modulations during sleep (which would be reflected by an augmentation of the sympathetic component of the LF/HF ratio and the LF band, and as seen in OSA+h patients only). Therefore, this possibility implies that only certain subjects with apneas would finally develop hypoxia. On the other hand, however, there could be a second possibility, in which all patients with apneas would develop hypoxia, but some of them (i.e., those with OSA−h) were assessed earlier in the course of their disease.

4.5. Limitations of this study

Whether OSA−h eventually evolves to OSA+h with hypoxia seems to be intuitive, although further prospective studies are required to confirm this, given that the design of our research is insufficient to answer this question. In addition to the anatomical features that may predispose OSA−h individuals to develop hypoxia, other hypotheses (such as polyneuropathy of the upper airway nerve endings induced by apnea that aggravates the mechanoreceptor function (Friberg et al., 1998)) must be taken into account.

There remain other mechanisms that are possibly relevant in OSA pathophysiology that could be studied here. These include surface tension forces (Kirkness et al., 2003), body-head position (Ong et al., 2011), hormonal effects (Killick et al., 2013), or the role of hypercapnia. In addition to afferents from respiratory mechano-

receptors, increases in CO_2 can induce arousal in humans in the absence of changes in respiratory mechanoreceptors activity (Ayas et al., 2000). Regrettably, we were unable to measure the CO_2 changes during sleep in our patients.

As mentioned before, a prominent percentage of OSA−h patients had previously undergone ENT surgery. If, prior to the interventions, these patients were suffering from OSA+h, it would confirm the notion that the biomechanical features are crucial for the emergence of hypoxia, and, therefore, would be intimately related to the sympathetic dysfunction seen in these patients. Besides, other covariates potentially related to the ENT surgery (e.g., socioeconomic status or other demographic features) could also contribute to the observed differences between OSA+h and OSA−h. However, as most of the interventions were performed elsewhere, data about the previous demographic or sleep features could not be gathered. We repeated the sleep characteristics analysis after excluding the 20 OSA−h patients with a previous history of ENT surgery. Differences remained essentially the same, although apnea duration tended to increase (23.45 ± 3.12 s), which suggests that ENT surgery might contribute to decreased apnea duration.

It is also worthwhile to point out the limitations of the HRV analysis, particularly the LF band and the LF/HF ratio, to measure cardiac autonomic function. Although both indexes have been considered measures of sympathetic activity, recent data clearly demonstrate that these measures reflex sympathetic and parasympathetic activity (Reyes del Paso et al., 2013). Also, although we used a sampling rate of 250 Hz (which is accepted by the current HRV standards of measurements), the optimal sampling rate is 1000 Hz in order to precisely determine the R-wave fiducial point (Task Force, 1996).

We aimed to select a homogenous sample, free from medications, cardiovascular disease and other comorbidities, to reliably assess the HRV. However, further research may extend our results taking into consideration a more realistic sample, including patients with hypertension and diabetes. Moreover, in this preliminary report we did not investigate the putative therapeutic implications of our results (e.g., whether OSA−h patients have a distinct response to CPAP therapy) and did not evaluate prospective outcomes (e.g., whether cardiovascular mortality or sudden death frequency is different in both groups). This would be an appealing investigation, as OSA patients are more likely to experience sudden death at night (from 12 am to 6 am) than those without OSA, who are more likely to die between 6 am and 12 pm. The risk of sudden death in OSA is directly related to the severity of the AHI (Gami et al., 2005). The exact mechanism of this phenomenon is difficult to discern, although it is likely related to autonomic disarrangements. Interestingly, impaired baroreflex function (as measured by the LF component of the HRV) and tonic vagal heart rate control (as measured by the HF component of the HRV) have been reported as markers of increased risk of sudden death (La Rovere et al., 2001, 2003). If sudden death was essentially related to the hypoxia *per se* it would be then reasonable to hypothesize that its frequency would be higher in OSA+h when compared to OSA−h, regardless of the AHI. This should be ascertained in future research.

5. Concluding remarks

In summary, the physiopathology of OSA varies among patients. OSA patients exhibit distinct clinical, respiratory and autonomic features depending on whether they suffer from hypoxia. Our results open the door to appealing questions such as whether both groups of OSA patients are different in terms of response to CPAP therapy or incidence of vascular events. Additional approaches that can easily and reliably delineate the different features in clinical practice will be essential. Further research must deal with these queries.

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